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Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis

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Abstract

Data on the prevalence and causes of community-acquired bloodstream infections in Africa are scarce. We searched three databases for studies that prospectively studied patients admitted to hospital with at least a blood culture, and found 22 eligible studies describing 58 296 patients, of whom 2051 (13.5%) of 15 166 adults and 3527 (8.2%) of 43 130 children had bloodstream infections. 1643 (29.1%) non-malaria bloodstream infections were due to *Salmonella enterica* (58.4% of these non-typhoidal *Salmonella*), the most prevalent isolate overall and in adults, and 1031 (18.3% overall) were due to *Streptococcus pneumoniae*, the most common isolate in children. Other common isolates included *Staphylococcus aureus* (531 infections; 9.5%) and *Escherichia coli* (412; 7.3%). *Mycobacterium tuberculosis* complex accounted for 166 (30.7%) of 539 isolates in seven studies that used mycobacterial culture techniques. HIV infection was associated with any bloodstream infection, particularly with *S enterica* and *M tuberculosis* complex bacteraemia. Where recorded, patients with bloodstream infections had an in-hospital case fatality of 18.1%. Our results show that bloodstream infections are common and associated with high mortality. Improved clinical microbiology services and reassessment of empirical treatment guidelines that account for the epidemiology of bloodstream infections might contribute to better outcomes.

Introduction

Febrile illness is a leading reason for admission to hospital in Africa,[1–4] and rates of febrile illness are fuelled by the HIV epidemic.[5–9] Despite the major contribution of infectious diseases to hospital admission, the availability of diagnostic microbiology services for bloodstream infections other than malaria is often limited by cost, infrastructure, and personnel constraints.[10,11] Consequently, health-care workers must often rely on syndrome-oriented empirical approaches to treatment and might underestimate or overestimate the likelihood of certain diseases, risking poor clinical outcomes and the promotion of

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Search strategy and selection criteria: These are detailed in the Methods section.

antimicrobial resistance.[12–14] Understanding the causes and prevalence of community-acquired bloodstream infection, which is associated with high risk of death, can inform efforts to improve health outcomes in Africa and promote the meeting of millennium development goals for the reduction of child mortality and HIV/AIDS, malaria, and tuberculosis.

Early studies of bloodstream infections in children admitted to African hospitals suggest that the prevalence of bacterial bloodstream infections among inpatients with fever or clinical sepsis exceeds that described in wealthier regions[2,15–18] and that bacteraemia is a common cause of illness both in areas of high and low malaria prevalence. Gram-negative organisms, particularly *Salmonella enterica*, rival or exceed Gram-positive organisms in importance in several published reports on bloodstream infections in both adults and children from African countries.[19–22] In recent years, use of blood culture to assess seriously ill patients infected with HIV has led to a growing understanding of their increased risk of a range of invasive bacterial and fungal diseases, including *Streptococcus pneumoniae*, disseminated tuberculosis, cryptococcosis, and *Salmonella* bacteraemia caused by non-typhoidal *Salmonella*.[4,23–27]

We sought to review studies that used blood culture to identify non-malaria bloodstream infections among prospectively sampled adults and children with predefined, replicable, inclusion criteria admitted to hospitals in Africa, and then to aggregate these data to better quantify the prevalence of bloodstream infections and document the most commonly isolated organisms overall and among different subgroups. We postulated that bloodstream infections would be identified among many patients admitted to hospital in Africa, *S enterica* would be among the most commonly isolated pathogens, and that age, presence of HIV infection, and features of illness would affect the prevalence of bloodstream infections and predominant organisms isolated.

Methods

Search strategy and selection criteria

We searched two major scientific databases (PubMed and Embase) and one topical database (African Healthline) with terms defined with the assistance of a library science technologist (Megan Von Isenburg). PubMed was searched with the search string: “Africa and (fever or fevers or bacteremia or bacteremias or septicemia or septicemias) limit humans”. Embase was searched by use of the terms: “Africa” (exploded to all subheadings) and “fever/” or “fever.mp” or “fevers.mp” or “bacteremia/” or “bacteremia.mp” or “bacteraemia.mp” or “bacteremias. mp” or “septicemia/” or “septicemia.mp” or “septicaemia. mp” or “septicemias.mp”. Results were limited to humans. African Healthline was searched by use of the string: “Africa and (fever* or bacteremia* or septicemia*) limit humans and scholarly (peer reviewed) journals”. Abstracts and titles from all years and in all languages—translated though services provided by the search engines as needed—were compiled in Endnote (Thomson Reuters) and reviewed individually by two investigators (EAR and AVS) with a goal to locate articles that seemed to report on the use of bacterial blood culture to assess patients admitted to hospital. All articles flagged by either investigator as possibilities for inclusion were retrieved in full text and their references were again independently assessed by the same two investigators by use of PubMed to obtain abstracts as needed. Each article identified by this process as a candidate for inclusion was retrieved as full text. A checklist of predetermined inclusion and exclusion criteria was developed by all three authors and was used for independent assessment each of the full-text articles by two of the three authors (EAR and AVS). After both of these investigators had made a decision on inclusion versus exclusion, any disagreement was resolved through independent review by the third investigator. Full-text articles in French were read by two of the three

investigators (JAC and EAR). The names of the authors of candidate articles were not masked. Conference abstracts were not included in this review, because during the selection process it was noted that inclusion criteria (subjective *vs* predefined, retrospective *vs* prospective) were not often precisely defined in abstracts and therefore determination of important selection biases would not be possible. A systematic means by which to search for reliable so-called grey literature or unpublished reports on this topic was not available.

Included studies were required to be prospective, to recruit systematically or consecutively sampled paediatric or adult hospital admissions, and to evaluate all admissions, all febrile admissions, or all febrile admissions without a focus of infection using, at least, an aerobic blood culture. Studies specifying use of predefined criteria that included afebrile patients with suspected infections in addition to febrile patients were also included.

During abstract review, we excluded articles that investigated a single or narrow cause of febrile illness; studies with the primary goal of investigating diagnostics or treatments; and review articles, editorials, policy statements, and behavioural research. We also excluded articles describing illness in people living outside the African continent (eg, returned travellers), articles that only assessed bloodstream infections in specific risk groups (eg, sickle-cell anaemia), non hospital-based studies, retrospective analyses, case reports, studies focused on nosocomial infections, and studies during an epidemic or outbreak.

During full-text review, we excluded studies that examined specific risk populations or used retrospective inclusion techniques (eg, bacteraemia as the trigger for study entry), and those that used subjective or poorly defined inclusion criteria. Articles in which separation of outpatient and inpatient cohorts was not possible, and those that reported on patient cohorts already included in another more comprehensive study were excluded. We also excluded articles that did not distinguish between community-acquired and nosocomial infections. All articles were required to quantify the total number of blood cultures obtained and the total number of pathogenic isolates, as well as to identify the three most commonly isolated pathogens and detail the numbers of patients from whom these pathogens were isolated. If incomplete data or unclear methods precluded article inclusion, authors were contacted through the contact information provided by the article or obtained though internet search engines. Only studies meeting our minimum requirements for data completeness described above were included.

Validity assessment

Study validity was established by use of the selection criteria described above, thereby excluding studies that were thought likely to have invalid results or whose results could not be compared with studies included in the analysis. We expected variability to exist between microbiological techniques and interpretation of culture results, and that such variability probably reflects realities of studies of this type done in resource-limited settings. Therefore studies were not excluded on the basis of having used media and transport techniques that might have limited the isolation of fastidious pathogens. Studies were also not excluded on the basis of lack of detailed reporting of contaminants; however, the prevalence of possible contaminants among the organisms described as pathogenic was recorded and its possible effect on the prevalence of bloodstream infections is discussed. Heterogeneity was controlled primarily by specifying the use of predefined inclusion criteria. However, since the goal of the review was to broadly assess prevalence and type of community-acquired bloodstream infections across Africa, it was important that included articles encompassed expected diversity in different hospital communities (eg, academic, government, rural, urban) without focusing too narrowly on specific patient groups at risk for bloodstream infections (eg, patients in whom treatment for malaria had already failed).[28] Subgroup analyses were done to explore the effect of heterogeneity on the overall prevalence or

predominant types of bloodstream infections. Publication bias was not systematically calculated, since negative studies would be extremely unlikely and no standard for measuring expected prevalence of bloodstream infections in Africa exists. However, the possibility of publication bias in exaggerating the prevalence of bloodstream infections is discussed qualitatively.[29]

Data extraction

Descriptive and quantitative data from each paper were extracted individually by two investigators (EAR and AVS) and entered into a Microsoft Excel 2007 spreadsheet; this included hospital setting and location, region of Africa according to regional groupings detailed within the UNAIDS epidemic update 2007,[30] study time frame, specific inclusion or exclusion criteria, and culture techniques. Quantitative data collected included number of patients, age range, pathogens and contaminants isolated, antimicrobial susceptibilities, and use of additional tests (eg, for HIV or malaria). Paediatric studies were defined as those in which all included patients were younger than 15 years; studies with mixed populations of adult and children were analysed as adult studies. Inconsistencies between investigators after data extraction were resolved by return to the original papers.

Statistical analysis

Data on individual patients were compiled and analysed in aggregate to compare prevalence of bloodstream infections across studies and among different subpopulations. Analyses of associations between types of patients or clinical conditions (eg, HIV) and specific bloodstream infections were only done for studies in which full data were available for both the pathogens and factors being assessed; no data were imputed for any analyses. The χ^2 test or Fisher's exact test for frequencies less than five was used to establish the significance of associations made to bloodstream infections or specific causative organisms; values were expressed as odds ratios (ORs) calculated with JMP statistical software version 7•0.

Results

The online database search done on June 11, 2009, yielded 10 412 articles, 7596 of which were unique articles located in at least one of the three databases (figure 1): 3366 were unique to PubMed, 1244 unique to Embase, and 180 unique to African Healthline. Most of these articles were excluded on the basis of a primary topical focus other than assessment of suspected infection in patients admitted to hospital; others were excluded because of the type of study or population. 87 full-text articles (two in French, the rest in English) were obtained for more detailed evaluation;[2–4,14,15,17,19–24,26,27,31–103] one of these had been identified through a review of references.[85]

65 articles were excluded during detailed screening. Among the excluded articles 20 were excluded because they described analysis of patient cohorts with specific risks for bloodstream infections,[25,27,31,35,36,44,45,47,52,54,59,61,62,65,68,74,75,94,98,101] 12 for retrospective data collection,[33,37,41,49,53,55,64,69,73,84,89,96] and 11 for subjective, non-replicable, inclusion criteria.[15,17,35,55,66,71,77,82,84,91,95] 22 selected articles, representing 23 unique patient cohorts, were eligible for systemic review.[2,4,14,19,21–23,26,32,38,40,43,46,48,57,58,60,67,79,86,88,92] One article described results from two distinct cohorts,[88] and one article was included after provision of additional data from the authors (Enwere G, WHO, Geneva, Switzerland, personal communication).[58] For other articles excluded because of incomplete data, attempts to contact the authors were unsuccessful or data were not available.

The 22 eligible studies were done in 34 locations between 1984 and 2006 (table 1), and included 61 327 patients from southern (23 893 patients; 39•0%), east (21 317; 34.8%), north (10 230; 16.7%), and west and central (5887; 9.6%) Africa. 45 899 patients (74.6%) were from exclusively paediatric cohorts. Figure 2 shows the study locations and the three leading causes of non-mycobacterial bloodstream infection. Of the 61 327 patients, 43 741 (71•3%) were recruited from rural district or missionary hospitals, 7456 (12•2%) from urban hospitals and referral centres, and 10 130 (16•5%) from a public infectious disease hospital system in rural and urban areas. Basic inclusion criterion was hospital or ward admission for 40 228 patients (65•6%), fever without apparent focus of infection for 11 249 (18•3%), and fever or specific signs of infection for 9850 (16•1%).

All studies described the microbiological techniques used, although culture media and methods of identification of organisms varied between studies. Minimum acceptable culture volumes ranged from 1 mL to 3 mL in paediatric studies and from 5 mL to 18 mL in adult studies that provided this information.[4,14,22,23,26,32,46,48,57,67,79,86,92] Only two paediatric studies detailed the actual volume of specimens received from patients.[14,48]

Blood culture results were available for 58 296 (95•1%) of the 61 327 patients across all studies, and 5578 (9•6%, range 4•2–38•2%) had bacterial or fungal bloodstream infections. Of patients from seven studies that used both aerobic and mycobacterial culture techniques 513 (25•3%) of 2025 patients had bacterial or fungal bloodstream infections.[4,21,23,26,38,40,46] A total of 5647 non-malaria pathogic isolates were recovered across all studies: 3286 (58•2%) were Gram negative and 1885 (33•4%) were Gram positive (table 2). *S enterica* serotypes were the most commonly isolated pathogens, accounting for 1643 (29•1%) of isolates recovered overall, and 878 (42.3%) of pathogenic isolates among adults. *S enterica* serotypes were the second most prevalent organisms cultured from children, constituting 765 (21.4%) of 3569 pathogenic isolates in children. Across the whole sample, non-typhoidal serotypes (960 isolates; 17•0%) were more commonly isolated than were *S enterica* serotype Typhi (560; 9•9%), and 507 (90•5%) of the *S enterica* serotype Typhi isolates were from patients in the two north African studies.[32,67] Among 960 non-typhoidal *Salmonella* isolates, 706 (73•5%) were serotyped; *S enterica* serotype Typhimurium was the most prevalent non-typhoidal *Salmonella* accounting for 460 (65•2%) of serotyped isolates, then *S enterica* serotype Enteritidis with 234 (33•1%). 688 (12•2%) of the isolates were non-*Salmonella* Enterobacteriaceae, 412 (59•9%) of which were *Escherichia coli. Haemophilus influenzae* constituted 287 (5•1%) of isolated organisms, 124 of which (82•1% of 151 documented to have been subtyped) were *H influenzae* type B. *Brucella* spp were identified in 275 (4•9%) of the positive blood cultures, all from one north African study.[32]

Among prevalent Gram-positive organisms, *Streptococcus pneumoniae* accounted for 1031 (18•3%) of the isolates, and was the most common isolate in children, constituting 833 (23.3%) of the paediatric pathogens. *Staphylococcus aureus* constituted 537 (9•5%) of the total isolates across the age spectrum. Fungi accounted for 40 (0•7%) of the isolates. Most fungal isolates were *Cryptococcus* spp (29 *Cryptococcus neoformans* and one *Cryptococcus laurentiae*).

Of all included children, 3527 (8•2%) of 43 130 had bloodstream infections, compared with 2051 (13•5%) of 15 166 adults (OR 0•60, p<0•0001). HIV infection was diagnosed in 499 (18•5%) of 2695 tested patients in paediatric studies compared with 1217 (53•5%) of 2273 tested patients in adult studies (OR 0•20, p<0•0001). Compared with adults, bacteraemia in children was more likely to be caused by Gram-positive organisms (OR 1•6, p<0•0001), including *S pneumoniae* (OR 1•5, p<0•0001), *S aureus* (OR 1•4, p<0•0001), and group A streptococci (OR 10•8, p<0•0001), or by non-*Salmonella* Enterobacteriaceae (OR 1•4, p<0•0001). *H influenzae* infection was found almost exclusively in children (OR 101•2,

p<0·0001). *S enterica* (OR 3·4, p<0·0001), mycobacteria (OR 34·6, p<0·0001), and yeasts (OR 111·2, p<0·0001) predominated among adults (table 2).

Among the five adult studies that included mycobacterial blood-culture techniques, *M tuberculosis* complex was the most common isolate, accounting for 166 (33·8%) of 491 isolates from 1716 patients.[4,23,26,38,46] Four of these studies detailed data on polymicrobial bloodstream infections; 13 (8·5%) of 153 patients with *M tuberculosis* bacteraemia also had bacteraemia with another organism, most commonly non-typhoidal *Salmonella* (5; 39%) or *S pneumoniae* (4; 31%).[4,23,26,38] In the two paediatric studies which assessed for mycobacteraemia, one child had *Mycobacterium avium* complex bacteraemia, but *M tuberculosis* was not recovered from any child, despite bloodstream infections with other pathogens being identified in 12 (15.0%) of 80 and 35 (15.3%) of 229 included patients.[21,40] All of the children in these studies had previously received a BCG vaccination; cultures were obtained by drawing 3 mL of blood into BACTEC MYCO/F LYTIC blood culture bottles (Becton Dickinson Inc).

Organisms thought to be skin-flora contaminants were explicitly reported to have been excluded from the analyses in 17 studies;[2,14,19,21,23,26,32,38,40,48,57,58,60,67,79,86,92] in 11 studies providing full data, contaminants were isolated from 5448 (13·1%) of 41 443 paediatric blood cultures versus 47 (3·5%) of 1355 adult blood cultures (OR 3·8, p<0·0001).[2,14,19,23,26,38,48,57,79,86,92] In addition to the organisms reported to have been excluded, 137 (7·3%) of 1885 Gram-positive and 21 (0·6%) of 3286 of Gram-negative organisms were reported as pathogens justified by clinical scenarios, but could have been classified as contaminants in other studies. These included *27 Staphylococcus epidermidis* isolates, 109 *Streptococcus viridans* or unspecified streptococci, one *Bacillus cereus*, and 21 Gram-negative rods of the genera *Burkholderia*, *Aeromonas*, *Flavimonas*, *Flavibacterium*, and *Xanthomonas*. 132 (83·5%) of 158 possible contaminants were identified in paediatric studies. Additionally, Falade and colleagues[60] reported that 18 of 78 isolates of *S aureus* isolated from their cohort were sent to a reference laboratory for confirmation (the same laboratory used by Enwere and colleagues[58] in their analysis included in this study), but only one of the 18 was confirmed to be *S aureus*; the remaining 17 isolates were coagulase negative staphylococci. Confirmation for the remaining 60 isolates was not available.

13 studies reported the prevalence of malaria parasitaemia identified by thick or thin smear.[2,4,19,21,38,40,43,46,57,67,86,88,92] Of 21 131 patients for whom malaria film results were reported 11 914 (56·4%, range 5·7–61·7%) were parasitaemic; in five adult and two paediatric cohorts, prevalence of bacterial or fungal bloodstream infections was greater than the prevalence of malaria parasitaemia.[4,21,38,40,57,67,88] Among two adult and seven paediatric studies, 769 (6·5%) of 11 814 patients with parasitaemia also had fungal or bacterial bloodstream infections.[2,14,19,21,38,43,57,86,92]

Archibald and colleagues[38] in Dar es Salaam, Tanzania, and Bell and colleagues[46] in Lilongwe, Malawi, assessed the prevalence of malaria among febrile study patients compared with asymptomatic outpatients or people admitted to hospital with non-febrile disorders. Among patients from Lilongwe, parasitaemia was significantly more common (relative risk 2·3, p=0·0021) among study patients (72 [31%] of 231) compared with randomly selected afebrile outpatients (10 [14%] of 73), but there was no difference (p=0·575) in prevalence of parasitaemia between study patients (49 [9·5%] of 517) and afebrile patients admitted to the orthopaedic ward in Dar es Salaam (12 [8·0%] of 150). In a rural western Kenya cohort described by Dougle,[57] 197 (86.0%) of 229 study patients were smear negative for malaria, yet 137 (59.8%) of all 229 study patients had a primary diagnosis of malaria. Bloodstream infections were identified in 51 (22.3%) of the patients in this study, 35 (69%) of whom were diagnosed with malaria on admission.

In addition to blood culture, Afifi and colleagues[32] tested serum samples for *Brucella* spp by use of slide or tube agglutination with *Brucella abortus* antigens. Agglutination testing had a specificity of 79% and a sensitivity of 89% compared with growth in biphasic blood-culture media (PML Microbiologicals, Wilsonville, OR, USA). A positive serum agglutination test for *Brucella* spp in the absence of isolation in blood culture was identified in one of 336 patients in Petit and colleagues' 1990 cohort.[88] Only one article reported viral serology, and identified dengue as the most common cause of laboratory-identified febrile illness, accounting for 18 of 100 cases of fever without a focus in Port Sudan.[67] Okwara and colleagues reported urine culture results and found that ten (26•3%) of 38 children with urinary tract infection also had bacteraemia with the same organisms, most commonly with *Citrobacter* spp (five children; 50•0%) and *Enterococcus* spp (two children; 20•0%); these patients accounted for ten of 32 patients with bacteraemia in the study.[86]

Of 4968 patients from 11 studies that included HIV antibody testing, 1738 (35•0%) were HIV seropositive.[4,21,23,26,38,40,46,48,57,79,88] In seven studies with sufficient data for analysis, 486 (34•5%) of 1407 patients infected with HIV had bloodstream infections versus 110 (15•2%) of 725 people seronegative for HIV (OR 3•4, p<0•0001; table 3).[4,21,26,38,40,46,79] Infection with non-typhoidal *Salmonella* (OR 8•2, p<0•0001)[4,23,38,79] and *M tuberculosis* (OR 23•4, p<0•0001)[4,23,26,38,46] were significantly more likely among people infected with HIV than among uninfected patients in studies reporting sufficient data for analysis, whereas *S enterica* serotype Typhi bacteraemia was identified in fewer patients infected with HIV than uninfected patients (OR 0•07, p<0•0001).[23,26,38,79] *C neoformans* (21 patients) and *Histoplasma capsulatum* (two patients) were found exclusively in patients infected with HIV in studies where pathogen-specific HIV serostatus was provided.[23,26,38,46] Infection with *S pneumoniae*,[4,23,26,38,79] *S aureus*,[23,26,38,79] and *E coli*[4,23,26,38,57,79] were not associated with HIV infection among the studies in this Review.

Antimicrobial use before admission to hospital was common, ranging from 3% to 56% of patients across eight studies reporting such data.[2,21,23,26,43,46,48,86] In four studies,[21,23,43,86] receipt of antimicrobial drugs as an outpatient was not associated with blood culture results. One study[2] showed an increased risk of bacteraemia and one study identified fewer bloodstream infections in patients previously treated with antimicrobial drugs than in those who were not.[26]

13 studies, which included 3916 (69•3%) of the total pathogens isolated, reported results of antimicrobial susceptibility testing, all of which used disc diffusion or Etest methods.[2,22,23,26,32,38,46,57,58,60,79,88,92] Five of these studies specified use of interpretive criteria according to National Committee on Clinical Laboratory Standards guidelines (now the Clinical Laboratories Standards Institute).[38,58,60,88,92] Table 4 presents the major findings for prevalent isolates. Although 90•3% of *S pneumoniae* and 89•1% of *S enteria* serotype Typhi were classified as ampicillin susceptible, only 8•9% of *E coli* isolates were ampicillin susceptible. Susceptibility of *S enterica* serotype Enteritidis and *S enterica* serotype Typhimurium were 33•6% and 3•0% for ampicillin, 93•2% and 15•0% for co-trimoxazole, and 38•9% and 100% for chloramphenicol, respectively. More than 95% of Gram-negative organisms were susceptible to third-generation cephalosporins and ciprofloxacin.

Table 5 displays the clinical features associated with non-malaria bloodstream infections in at least two included cohorts. Clinical features significantly associated with bloodstream infections included lethargy, restlessness, oral candidiasis, and jaundice. Hepatomegaly and splenomegaly showed variable association with bloodstream infections across studies. Malnutrition, which was defined differently by different authors, correlated in some studies but not in others; four paediatric studies found an association between malnutrition and

bloodstream infection,[14,21,48,92] whereas two other paediatric and one adult study found no association or a negative association with malnutrition.[2,23,79]

The proportion of patients with bloodstream infections was greater among cohorts that restricted enrolment to patients with fever or other signs of infection versus all admissions (13•4% *vs* 7•4%; OR 1•9, p<0•0001) and in cohorts that included fever with or without a focus over those that included patients with non-focal febrile illness alone (16•6% *vs* 10•5%; OR 1•7, p<0•0001). Fever higher than 38•9°C was associated with bloodstream infections in four studies[4,14,19,46] but showed no relation in one.[43]

Mycobacteraemia was associated with chronic cough in two studies (OR 3•8–16•4, p<0•01).[4,26] However, 23 (38%) of 60 patients and 13 (23%) of 57 patients with mycobacteraemia from two studies had no associated respiratory signs or symptoms.[38,46] Three studies identified anaemia more often in patients with mycobacteraemia compared with all patients (OR 9•5, p<0•001),[4] all patients infected with HIV (p<0•001),[23] or all patients with bloodstream infections (p<0•05).[26]

16 studies reported in-hospital fatality for all enrolled patients with and without bloodstream infections; [2,4,14,19,21–23,26,32,43,46,48,67,79,88,92] 2703 (5•3%) of 51 346 died in hospital. In 13 reporting studies, [2,4,19,23,26,32,43,46,48,67,79,88,92] 700 (18•1%) of 3873 patients with bloodstream infections died in hospital compared with 1966 (4•4%) of 45 030 patients without bloodstream infections (OR 4•8, p<0•0001). 47 (42%) of 111 patients with mycobacteraemia died in hospital in four reporting studies.[23,26,38,46]

Associations between seasons and rates of bloodstream infection and prevalent organisms were described in seven studies.[14,32,19,40,46,58,92] Data from Malawian cohorts in both Blantyre and Lilongwe showed a shift from a predominance of non-typhoidal *Salmonella* during the wet season to a predominance of *S pneumoniae* during the dry season.[40,46] Enwere and colleagues[58] also noted an increased prevalence of *S pneumoniae* during the hot dry season in the Gambia, and Afifi and colleagues[32] showed a relation between how often *S enterica* serotype Typhi was isolated with the onset of the rainy season in Egypt from November through January. Factors other than rainfall might also have a role. In Egypt, *Brucella* spp were isolated most often from March to June, the period of livestock parturition.[32] Sigauque and colleagues[92] found no association between season and bloodstream infections.

Discussion

Bacterial or fungal bloodstream infections are common among prospectively sampled adults and children admitted to hospital in Africa, with a mean prevalence of 13•4% (range 8•5–38•2%) among those with fever and 7•4% (4•2–16•9%) among all admissions irrespective of fever history. These data underscore the importance of considering bacterial or fungal bloodstream infections in the differential diagnosis of all patients admitted to hospital, particularly those who are febrile. Our findings suggest that health outcomes in Africa could be improved by scale-up of laboratory facilities to allow for accurate diagnosis and directed treatment of patients with bloodstream infections and to inform local policy on likely prevalence, pathogens, and antimicrobial susceptibility patterns.

WHO guidelines for management of acute illness in children (Integrated Management of Childhood Illness) recommend use of an appropriate antibacterial drug in addition to an antimalarial drug in children with certain signs of severe illness.[104] However, the algorithm remains structured around malaria treatment even in areas of low malaria risk, recommending use of an antimalarial drug before clinical follow-up in febrile illness without focal signs. Our Review indicates that the presence of malaria parasitaemia does not exclude

bloodstream infection with other organisms, particularly in areas with high malaria prevalence. In the large paediatric cohort from Mozambique investigated by Sigauque and colleagues,[92] 621 (5.8%) of 10 699 children admitted to hospital with both tests available were found to have concomitant bacterial bloodstream infection with malaria parasitaemia.

The common practice of diagnosing and treating fever as malaria was described in Kenyan[57] and Malawian[46] cohorts included in this Review, and was also shown by Reyburn and colleagues[105] in Tanzania, who found that most (2412; 53•9%) patients treated for malaria in hospital were slide-negative, and that 1571 (66%) of these patients did not receive antibacterial drugs.[105] In the study by Reyburn and colleagues,[105] malaria slide-negative patients had a higher mortality than did slide-positive patients (6•9 *vs* 12•1%, p<0•001), suggesting that empirical treatment of malaria without subsequent treatment for other causes of febrile illness might have played a part in this excess mortality. Our Review suggests that *S enterica* is one of the pathogens most commonly isolated throughout various settings in Africa and, like malaria, *S enterica* bacteraemia can cause undifferentiated fever and splenomegaly. We have also shown that *M tuberculosis* bacteraemia can present without focal signs, although this has only been proven in adults. Taken together, this information presents a strong case that empirical treatment of malaria alone in regions of both high and low prevalence will result in inadequate management of a substantial portion of patients with non-malaria bloodstream infections.

HIV infection is linked to the distribution, prevalence, and cause of community-acquired bloodstream infections in patients admitted to hospital in Africa. Non-malarial bloodstream infection—particularly with non-typhoidal *Salmonella*, *M tuberculosis*, or fungi—was more prevalent in patients infected with HIV than in those without HIV, and might have also influenced the prevalence and distribution of types of bloodstream infections between adults and children, given that HIV infection was present much more commonly among adults. Among the five studies in adults that used mycobacterial blood-culture techniques,[4,23,26,38,46] *M tuberculosis* was the most common isolate, comprising just over one third of all bacterial and fungal bloodstream isolates. The vast majority of these patients were infected with HIV, and a substantial proportion of them did not present typical chest signs associated with tuberculosis disease.[38,46] In these patients, chronic fever and wasting were common and many had abnormal chest radiographs even in the absence of chest symptoms.[4,26,38] Knowledge of local HIV prevalence and routine HIV counselling and testing of patients admitted to hospital whose HIV status is unknown will assist health-care workers in formulating a differential diagnosis. Evidence suggests that even low levels of immune suppression can be associated with significantly increased risks of invasive bacterial disease.[106] The influence of expanded access to antiretroviral therapy programmes on the epidemiology of bloodstream infections in Africa is yet to be established.

Of note, bloodstream infection with *M tuberculosis* was not identified among the Malawian children described by Archibald and colleagues,[21,40] despite a high prevalence of HIV and other bloodstream pathogens. Blood-culture volume, effects of the BCG vaccine, or unique disease pathogenesis in adults and children might lead to this lack of association; this merits further investigation in other studies. Additionally, the inverse association between *S enterica* serotype Typhi bacteraemia and HIV is striking and further research to substantiate and explore this might reveal important immunological or epidemiological differences between different serotypes of *S enterica*.

With the exception of *E coli* and non-typhoidal *Salmonella*, pathogens included in this Review tended to be susceptible to one or more locally available antimicrobial drugs. However, the studies in which antimicrobial susceptibility was assessed were done between 3 years and 16 years ago and might not reflect current local patterns. Few (<30%) non-

typhoidal *Salmonella* isolated among studies in this Review were susceptible to ampicillin, most *S enterica* serotype Enteritidis were resistant to chloramphenicol, and most *S enterica* serotype Typhimurium were resistant to co-trimoxazole. Frequent isolation of non-typhoidal *Salmonella* resistant to commonly used antimicrobial drugs has been described by other investigators.[107–110] Additionally, meticillin-resistant *S aureus*,[32,111,112] penicillin-resistant *S pneumoniae*,[38,111] and multidrug-resistant Enterobacteriaceae and *M tuberculosis*[50,107,113,114] have been reported in Africa and present a threat to individual and public health. Most invasive bacterial isolates across all studies in this Review were susceptible to third-generation cephalosporins or fluoroquinolones. However, these drugs might be beyond the financial reach of patients and institutions, and their increased use as empirical treatment might promote antimicrobial resistance. Taken together, these data emphasise the complexity and potential pitfalls of attempting to treat common illnesses without improvement in directed diagnostics.

Vaccine-preventable diseases continue to cause a substantial burden of disease in Africa.[115,116] *S pneumoniae* was the most commonly isolated paediatric pathogen among patients in our Review, and invasive *H influenzae* (the majority of which was documented to be the vaccine-preventable type B), was found in 286 (8.0%) children with bloodstream infections. Enhanced uptake of available vaccines and increased pathogen surveillance should be prioritised to optimise benefits from vaccines and to inform their further development. Given the prevalence of non-typhoidal *Salmonella* among patients in this Review, further research into vaccine development is crucial.[117]

There are several important limitations to this study. We examined hospital-based cohorts to define community-acquired bloodstream infections, and thereby might have included patients with more severe illness and included only those who have access to health-care facilities.[118] However, non-malaria bloodstream infection might be as common among certain groups of outpatients as in inpatients in Africa.[14,39,70] Some important features related to the risks and clinical importance of bloodstream infections in different groups of patient (eg, infants *vs* older children, patients with underlying clinical conditions other than HIV, patients with HIV across the spectrum of immune suppression) were not explored in this study. Enrolment and inclusion criteria varied by study, and studies spanned a period of more than 20 years; therefore overall prevalence of bloodstream infection and the types of organisms isolated should not be seen as a guide to diagnosis for individual clinical encounters, rather as an indication of the anticipated range of pathogens and to emphasise the need to consider the most locally appropriate treatment for a patient who might have a bloodstream infection. Aggregation of raw data resulted in weighting of large studies; the local importance of some pathogens isolated in smaller studies might have been underrepresented.

Some pathogens were either incompletely identified or incompletely reported (4.7% of all pathogens reported); these might have been bloodstream contaminants and might have resulted in an enhanced estimate of the true prevalence of bloodstream infections. Studies varied in how a blood-culture contaminant was defined, and as was noted by Falade and colleagues,[60] the prevalence of *S aureus* as a pathogen and of bloodstream infection as a whole might have been overestimated by some laboratories incorrectly identifying coagulase-negative staphylococci as *S aureus*. Underestimation of bloodstream infections could have occurred as well, because the diagnostic sensitivity of the laboratory techniques used in various studies could not be rigorously assessed, and fastidious pathogens that need optimum culture and transport methods might not have been isolated in some laboratories. Commonly isolated organisms, such as *S pneumoniae* and *H influenzae*, might have been underestimated due to their fastidious nature. Bloodstream infection in children, in particular, might also have been underestimated as a result of blood-culture volume

inadequacy. On analysis of blood volume from 16 570 cultures from children, Berkley and colleagues[48] noted increased prevalence of bloodstream infection (7·9%) in 3 mL samples compared with 1 mL samples (5·6%, p=0·006).

Studies that found high prevalences of bloodstream infections might have been preferentially published over other studies. However, the exclusion of studies that enrolled patients who were subjectively defined as "septic" probably reduced the degree of bias presented in this Review. Patterns of vaccine use might have influenced the prevalence and types of pathogens isolated; the cohort presented by Enwere and colleagues[58] was part of a study to assess the efficacy of the pneumococcal vaccine.

This Review presents a strong case for the importance of considering non-malarial bloodstream infections in all patients admitted to hospital in Africa, particularly those with fever, known HIV infection, signs of impaired immunity, or lethargy. Our findings underscore the importance of continuous re-evaluation of WHOs Integrated Management of Childhood Illness and other empirical treatment algorithms for febrile illness in view of changing patterns of disease. When used, empirical treatment with antimicrobial drugs should include coverage for Gram-negative and Gram-positive organisms, and be effective against *S enterica* and *S pneumoniae*. Furthermore, our Review highlights that the prevalence of bacteraemia exceeds the prevalence of malaria parasitaemia among patients admitted to hospital in some regions, and that malaria parasitaemia and bacteraemia might coexist. Therefore, clinicians should be alert to local malaria transmission patterns and maintain a high index of suspicion for bacteraemia when proceeding though a diagnostic and treatment plan for an ill patient with a blood film showing malaria in a region of high prevalence. Public health leaders should prioritise the use of available vaccines, and consider means to alleviate the direct cost of antimicrobials to patients admitted to hospital. Further resources and research to define risk factors and prevention strategies, including vaccines, for non-typhoidal *Salmonella* in Africa are needed. Expanded and improved clinical microbiology services in Africa might contribute substantially to the improved management of community-acquired bloodstream infections. In the meantime, regular collection and dissemination of microbiological data from sentinel hospital studies, such as those included in the Review, are needed to inform empirical guidelines for management of patients with suspected community-acquired bloodstream infection.

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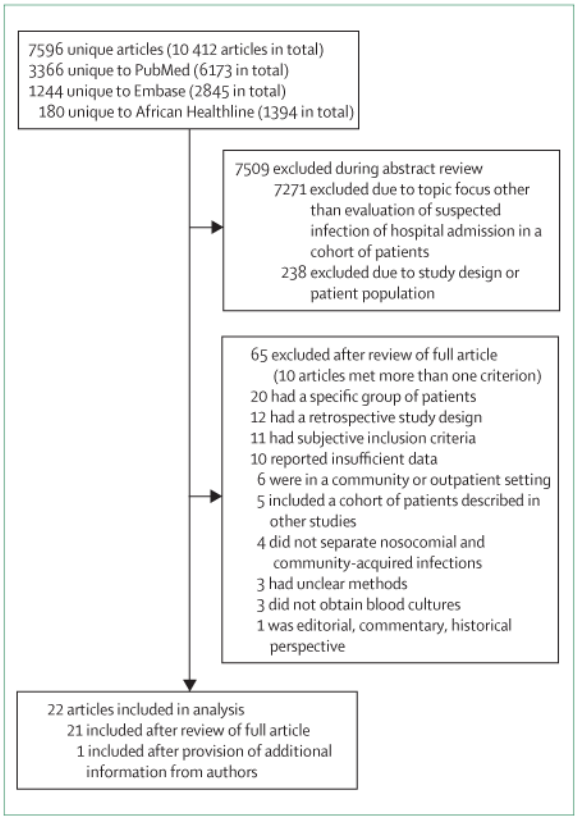

Figure 1. Selection of eligible articles

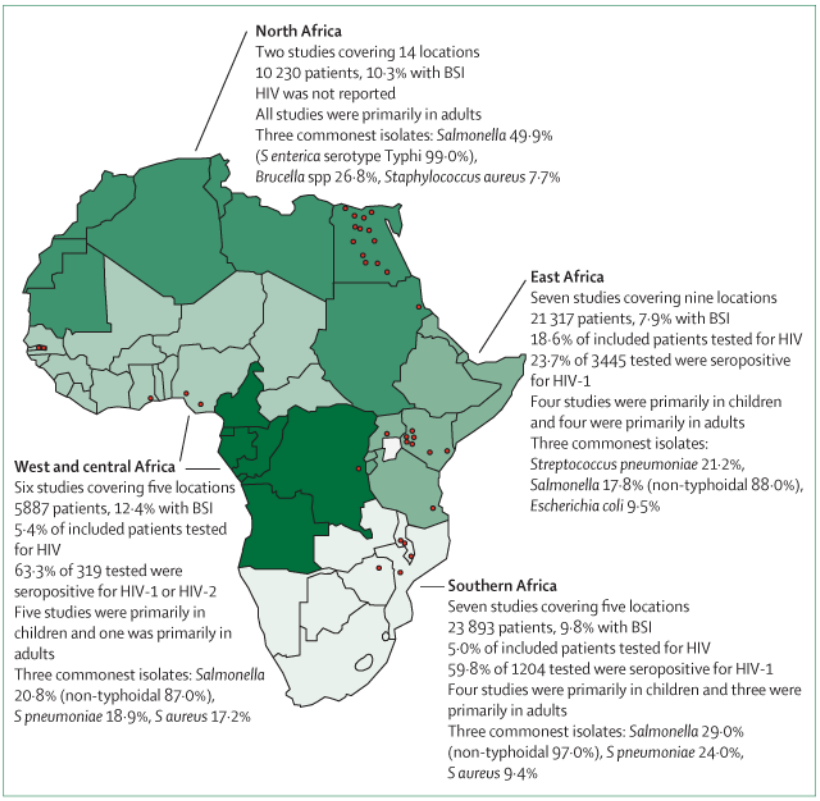

Figure 2. Study locations and summary findings including prevalent pathogens

Mycobacterium tuberculosis was excluded because adequate comparison of its relative importance could not be made since several study sites did not use culture media capable of isolating mycobacteria.

Table 1

Summary of 22 studies of community-acquired bloodstream infection (BSI) among patients admitted to hospital in Africa, 1984–2006

	Location; study dates	Hospital type	Age (population type)	Primary eligibility criteria	Other criteria	Temperature	Non-malarial BSI	Malarial BSI	Mycobacterial culture	Patients infected with HIV (proportion of patients tested)*	Most common isolates
Afifi et al[32]	Multiple locations, Egypt; 1999–2003	Public infectious disease hospitals	>4 years (primarily adults)	Fever without localising signs	Inclusion: suspect typhoid, brucellosis Exclusion: reported fever <2 days	38.5°C (oral, rectal)	1005 (10.2%)	..	No	..	*Salmonella enterica* serotype Typhi, *Brucella* spp, *Staphylococcus aureus*
Akpede et al[19]	Benin City, Nigeria; October, 1988, to October, 1989	Urban teaching hospital	1 month to 5 years	Fever without localising signs	Exclusion: severe malnutrition, chronic illness, fever >7 days	38.0°C (rectal)	67 (10.4%)	446 (69.5%)	No	..	*S aureus*, Enterobacteriacea (25% untyped), *Citrobacter* spp
Archibald et al[38]	Dar es Salaam, Tanzania; February to April, 1995	Urban referral and teaching hospital	≥15 years (primarily adults)	Fever	..	37.5°C (axillary)	145 (28.9%)	49 (9.8%)	Yes	282 (56.2%)	*Mycobacterium tuberculosis* complex, non-typhoidal *Salmonella*, *S enterica*
Archibald et al[40]	Lilongwe, Malawi; March to April, 1998	Urban government hospital	≤13 years (primarily children)	Fever	Inclusion: BCG vaccination	37.5°C (axillary)	12 (15.0%)	15 (18.8%)	Yes	25 (31.3%)	Non-typhoidal *Salmonella*, *Escherichia coli*, *S enterica* serotype Typhi, *S aureus*
Archibald et al[21]	Lilongwe, Malawi; July to August, 1998	Urban government hospital	1 month to 13 years (primarily children)	Fever	Inclusion: prescription of antimicrobial drugs by admitting HCP	..	35 (15.3%)	13 (5.7%)	Yes	63 (28.0%)	Non-typhoidal *Salmonella*, *E coli*
Ayoola et al[43]	Ibadan, Nigeria; June to November, 1998	Urban referral and teaching hospital	1–12 months (primarily children)	Fever	Exclusion: antibiotic preceding 7 days	38.0°C (rectal)	39 (38.2%)	47 (46.1%)	No	..	*E coli*, *S aureus*, *Klebsiella* spp
Bahwere et al[2]	Lwiro, DR Congo; January, 1989, to December, 1990	Rural children's hospital	Unspecified (primarily children)	All hospital or ward admissions, irrespective of fever	..	..	124 (15.9%	182 (28.8%)	No	..	Non-typhoidal *Salmonella*, *E coli*, *Citrobacter* spp
Bell et al[46]	Lilongwe, Malawi; March to May, 1998	Urban government hospital	≥14 years (primarily adults)	Fever	..	37.5°C (axillary)	67 (28.2%)	72 (31.2%)	Yes	173 (72.7%)	Non-typhoidal *Salmonella*, *M tuberculosis* complex, *Cryptococcus* spp
Berkley et al[48]	Kilifi, Kenya; August, 1998, to July, 2002	Rural district referral hospital	<13 years (primarily children)	All hospital or ward admissions, irrespective of fever	Exclusion: elective procedures, minor injuries	..	1094 (6.6%)	..	No	243 (11.7%)	*Streptococcus pneumoniae*, non-typhoidal *Salmonella*, *Haemophilus influenzae*
Brent et al[14]	Kilifi, Kenya; May to October, 2003	Rural district referral hospital	0–5 years (primarily children)	All hospital or ward admissions, irrespective of fever	Exclusion: admission preceding 10 days	..	9 (4.2%)	..	No	..	*S pneumoniae*, *S aureus*
Dougle et al[57]	Mumias, Kenya; July to October, 1994	Rural missionary hospital	≥5 years (primarily adult)	Fever	..	38.0°C (axillary)	51 (22.3%)	25 (11.0%)	No	51 (22.5%)	*S enterica* serotype Typhi, non-typhoidal *Salmonella*, *S pneumoniae*
Enwere et al[58]	Basse and Bansang, Gambia; August, 2000, to April, 2004	Rural hospital	2–29 months (primarily children)	Fever	Inclusion: pneumonia, meningitis, suspect pyomyositis	38.0°C	248 (8.7%)	..	No	..	*S pneumoniae*, *S enterica*, *H influenzae*
Falade et al[60]	Ibadan, Nigeria; February, 2005, to January, 2006	Urban teaching, maternity, and state hospitals	2–59 months (primarily children)	Suspect pnuemococcal disease	Inclusion: standard case definition pneumonia, meningitis, or sepsis	..	222 (18.3%)	..	No	..	*S aureus*, *Klebsiella* spp, *S enterica*
Gordon et al[22]	Blantyre, Malawi; December, 1997, to November, 1998	Urban government referral and teaching hospital	14–76 years (primarily adults)	Fever	..	37.5°C	449 (16.1%)	..	No	..	Non-typhoidal *Salmonella*, *S pneumoniae*, *E coli*
Hyams et al[67]	Port Sudan, Sudan; January, 1984	Urban government hospital	≥12 years (primarily adults)	Fever without localising signs	.	37.8°C†	22 (22.0%)	13 (13.0%)	No	..	*S enterica* serotype Typhi, *S enterica* serotype Paratyphi A, *Streptococcus pneumoniae*
Nathoo et al[79]	Harare, Zimbabwe; June, 1993, to December, 1994	Urban referral hospital for municipal clinics	0–8 years	Fever	Inclusion: pneumonia, meningitis, other signs acute infection	38.0°C (axillary) r	95 (30.7%)	..	No	168 (54.4%)	*Staphylococcus epidermidis*, *S aureus*, *S pneumoniae*
Okwara et al[86]	Nairobi, Kenya; January to March 2001	Urban public teaching hospital	3 months to 12 years	Fever without localising signs	Exclusion: severe malnutrition, chronic illness	37.5°C	32 (12.1%)	158 (59.8%)	No	..	Non-typhoidal *Salmonella*, *Citrobacter* spp, *S aureus*, *Enterococcus* spp
Peters et al[4]	Blantyre, Malawi; February to May, 2000	Urban government referral and teaching hospital	≥14 years (primarily adults)	Fever	Inclusion: shock (HR ≥120, SBP <100); reported fever	37.4°C (axillary)	128 (36.4%)	69 (19.6%)	Yes	291 (82.7%)	*M tuberculosis* complex, non-typhoidal *Salmonella*, *S pneumoniae*

	Location; study dates	Hospital type	Age (population type)	Primary eligibility criteria	Other criteria	Temperature	Non-malarial BSI	Malarial BSI	Mycobacterial culture	Patients infected with HIV (proportion of patients tested)*	Most common isolates
Petit et al[88]	Mukumu, Kenya (study I); 1990	Rural hospital	>8 years (primarily adults)	Fever	..	38.0°C	25 (7.4%)	104 (31.0%)	No	12 (3.6%)	*S enterica*, *Acinetobacter* spp, *Pseudomonas aeruginosa*
Petit et al[88]	Rural Westem Kenya (study III); 1987	Rural hospital	>8 years (primarily adults)	Fever without localising signs	Exclusion: reported fever <2 days	38.0°C	33 (29.2%)	22 (27.5%)	No	..	*Proteus mirabilis*, *S enterica*, *S aureus*
Sigauque et al[92]	Manhiça, Mozambique; May, 2001, to April, 2006	Rural district referral hospital	<15 years	All hospital or ward admissions, irrespective of fever	Exclusion: trauma	..	1550 (7.8%);	17354 (61.6%)	No	..	Non-typhoidal *Salmonella*, *S pneumoniae*, *S aureus*
Ssali et al[26]	Kampala, Uganda; January to April, 1997	Urban public teaching hospital	15–65 years (primarily adults)	Fever	..	38.0°C (axillary)	72 (23.6%)	..	Yes	228 (76.3%)	*M tuberculosis* complex, *S pneumoniae*, *S enterica*
Vugia et al[23]	Abidjan, Côte d'Ivoire; May to June, 1991	Urban referral hospital	Unspecified (primarily adults)	All hospital or ward admissions, irrespective of fever	Inclusion: admitted to hospital ID service	..	54 (16.9%)	..	Yes	202 (63.3%)	*S enterica*, *M tuberculosis* complex, *E coli*

*Archibald et al[21] included 30 infants <18 months seropositive for HIV alone; Nathoo et al[79] included 61 infants <18 months seropositive for HIV with clinical immunosuppression; Vugia et al[23] included 139 patients infected with HIV-1, 22 infected with HIV-2, and 41 co-infected HIV-1 and HIV-2.

†Originally reported as 100°F.

Table 2
Blood culture isolates from 22 studies, Africa, 1984–2006

	Number of isolates (proportion of total isolates)	Number of isolates in adults (proportion of isolates in adults)	Number of isolates in children (proportion of isolates in children)
Enterobacteriaceae	2331 (41.3%)	1019 (49.0%)	1312 (36.8%)
Salmonella enterica	1643 (29.1%)	878 (42.3%)	765 (21.4%)
Non-typhoidal *Salmonella*[*]	960 (17.0%)	291 (14.0%)	669 (18.7%)
S enterica serotype Typhimurium	460 (8.1%)	185 (8.9%)	275 (7.7%)
S enterica serotype Enteritidis	234 (4.1%)	77 (3.7%)	157 (4.4%)
S enterica serotype Paratyphi A	9 (<1.0%)	5 (<1.0%)	4 (<1.0%)
S enterica serotype Choleraesuis	3 (<1.0%)	0 (0.0%)	3 (<1.0%)
S enterica serotype Typhi	560 (9.9%)	553 (26.6%)	7 (<1.0%)
Unspecified *Salmonella* spp	123 (2.2%)	34 (1.6%)	89 (2.5%)
Non-*Salmonella* Enterobacteriaceae	688 (12.2%)	141 (6.8%)	547 (15.3%)
Escherichia coli	412 (7.3%)	77 (3.7%)	335 (9.4%)
Klebsiella spp	123 (2.2%)	24 (1.2%)	99 (2.8%)
Enterobacter spp	47 (<1.0%)	0 (0.0%)	47 (1.3%)
Proteus mirabilis	28 (<1.0%)	17 (<1.0%)	11 (<1.0%)
Citrobacter spp	26 (<1.0%)	1 (<1.0%)	25 (<1.0%)
Shigella spp	22 (<1.0%)	10 (<1.0%)	12 (<1.0%)
Other Enterobacteriaceae[†]	30 (<1.0%)	12 (<1.0%)	18 (<1.0%)
Other Gram-negative organisms	955 (16.9%)	341 (16.4%)	614 (17.2%)
Haemophilus influenzae	287 (5.1%)	1 (<1.0%)	286 (8.0%)
Brucella spp	275 (4.9%)	275 (13.2%)	0 (0)
Acinetobacter spp	100 (1.8%)	16 (<1.0%)	84 (2.4%)
Pseudomonas spp	76 (1.3%)	15 (<1.0%)	61 (1.7%)
Neisseria spp	55 (1.0%)	22 (1.1%)	33 (<1.0%)
Alcaligenes xylosoxidans	11 (<1.0%)	1 (<1.0%)	10 (<1.0%)
Haemophilus parainfluenzae	10 (<1.0%)	0 (<1.0%)	10 (<1.0%)
Campylobacter spp	9 (<1.0%)	0 (<1.0%)	9 (<1.0%)
Vibrio cholerae	1 (<1.0%)	1 (<1.0%)	0 (0)
Other Gram negatives[‡]	21 (<1.0%)	6 (<1.0%)	15 (<1.0%)
Unspecified Gram negatives	110 (2.0%)	4 (<1.0%)	106 (3.0%)
Gram-positive organisms	1885 (33.4%)	336 (16.2%)	1549 (43.4%)
Streptococcus pneumoniae	1031 (18.3%)	198 (9.5%)	833 (23.3%)
Staphylococcus aureus	537 (9.5%)	111 (5.4%)	426 (12.0%)
Other streptococci[§]	118 (2.1%)	21 (1.0%)	97 (2.7%)
Group A streptococcus	95 (17%)	3 (<1.0%)	92 (2.6%)
Group B streptococcus	63 (1.1%)	0 (0.0%)	63 (1.8%)

	Number of isolates (proportion of total isolates)	Number of isolates in adults (proportion of isolates in adults)	Number of isolates in children (proportion of isolates in children)
Staphylococcus epidermidis	27 (<1.0%)	1 (<1.0%)	26 (<1.0%)
Enterococcus spp	8 (<1.0%)	1 (<1.0%)	7 (<1.0%)
Other Gram-positives[¶]	5 (<1.0%)	1 (<1.0%)	4 (<1.0%)
Unspecified Gram positives	1 (<1.0%)	0 (0.0%)	1 (<1.0%)
Yeasts	40 (0.7%)	39 (1.9%)	1 (<1.0%)
Cryptococcus spp	31 (<1.0%)	31 (1.5%)	0 (0)
Candida spp	5 (<1.0%)	5 (<1.0%)	0 (0)
Histoplasma capsulatum	2 (<1.0%)	2 (<1.0%)	0 (0)
Unidentified fungi	2 (<1.0%)	1 (<1.0%)	1 (<1.0%)
Mycobacteria	174	173	1
Mycobacterium tuberculosis complex	166	166	0
Other mycobacteria[//]	5	5	0
Mycobacterium avium complex	3	2	1
Total number of undescribed isolates[**]	262 (47%)	170 (8.2%)	92 (2.6%)
Total number of polymicrobial infections	69	27	42
Total number of isolates	5647	2078	3569
Total number of patients with blood culture	58 296	15 166	43 130

[*] Total non-typhoidal *Salmonella* were not consistently described to species level, thus total reported non-typhoidal *Salmonella* was greater than the sum of species.

[†] Other Enterobacteriaceae include: unspecified Enterobacteriaceae (22), *Kluyvera* spp (2), *Deftroide* spp (2), *Hafnia alvei* (1), *Morganella* sp (1), *Providencia* sp (1), and *Serratia plymuthica* (1).

[‡] Other Gram-negative organisms were *Burkholderia cepacia* (1), *Flavobacterium* sp (1), *Flavimonas* sp (1), *Sphingamonas* sp (1), *Aeromonas* spp (16), and *Xanthomonas maltophila* (1).

[§] Other streptococci were *Streptococcus viridans* (41), *Streptococcus bovis* (1), group C streptococci (5), group G streptococci (3), unspecified streptococci (68).

[¶] Other Gram-positive organisms include: *Rhodococcus* spp (3), *Bacillus cereus* (1), and *Actinomyces* sp (1).

[//] Other mycobacteria include: *Mycobacterium simiae* (1), other atypical mycobacteria (2), and unidentifi ed mycobateria (2).

[**] Total categorical pathogens are not completely described in seven studies. Afifi et al[32] reported 159 (1.5%) of isolates by a general list, as follows: *Escherichia coli, Enterobacter cloacae, Streptococcus viridans*, streptococcus group C and D, *Pseudomonas aeruginosa*, yeast, *Salmonella* group B, *Pseudomonas* spp, *Klebsiella pneumoniae, Acinetobacter*, and *Citrobacter*. Bell et al[46] reported total numbers of pathogens, but did not describe six (8.8%). Berkley et al[48] described 69 out of 91 “other Gram-negative” pathogens in a table, leaving 22 undescribed. Enwere et al[58] and Falade et al[60] reported 28 and 38 organisms, respectively, as “Other pathogens”. Ssali et al[26] reported three pathogens with unknown identity, and two that were likely contaminants (*Micrococcus* sp, *Moraxella catarrhalis*). Sigauque et al[92] described 118 “other organisms” in a footnote to the article's table 1; however, the organisms in the footnote add to 114, leaving four undescribed.

Table 3

Causes of bloodstream infection by HIV serostatus* in seven African studies, 1993–2004

	Total isolates (proportion of patients with BSI)	Number of patients infected with HIV (proportion of patients with BSI)	Number of patients not infected with HIV (proportion of patients with BSI)	OR for those infected with HIV
Bloodstream infection[4,21,26,38,40,46,79]	596 (26.6%)	486 (34.5%)	110 (13.1%)	3.4 (p<0001)
Staphylococcus aureus[23,36,38,79]	38 (4.5%)	18 (2.0%)	20 (3.6%)	p>0.05
Streptococcus pneumoniae[4,23,26,38,79]	66 (3.7%)	48 (4.1%)	18 (3.0%)	p>0.05
Non-typhoidal *Salmonella*[4,23,38,79]	99 (6.7%)	92 (9.7%)	7 (1.3%)	8.2 (p<0001)
Salmonella enterica serotype Typhi[23,26,38,79]	8 (0.7%)	1 (0.1%)	7 (1.8%)	0.07 (p<0001)
Non-*Salmonella* Enterobacteriaceae[4,23,26,38,57,79]	50 (3.8%)	34 (3.8%)	16 (3.8%)	p>0.05
Escherichia coli[4,23,26,38,57,79]	30 (1.6%)	21 (1.8%)	9 (1.5%)	p>0.05
Mycobacterium tuberculosis complex[4,23,26,38,46]	166 (12.4%)	161 (17.9%)	5 (1.1%)	23.4 (p<0001)

BSI=bloodstream infections.

*Archibald et al[38] included 30 infants <18 months with HIV seropositivity alone; Nathoo et al[79] included 61 infants <18 months seropositive for HIV with clinical immunosuppression; Vugia et al[23] included 139 patients infected with HIV-1, 22 infected with HIV-2, and with 41 co-infected HIV-1 and HIV-2.

Table 4

Antimicrobial susceptibilities of common bloodstream isolates in seven reporting studies, Africa, 1993–2006

	Number of isolates*	Proportion of susceptible isolates (range of susceptibility)
Staphylococcus aureus[2,32,57,79,88,92]		
Ampicillin	220	9.1% (0–32%)
Chloramphenicol	195	64.6% (63–100%)
Co-trimoxazole	208	64.9% (18–100%)
Ceftriaxone	8	100.0% (100%)
Ciprofloxacin	8	100.0% (100%)
Gentamicin	213	93.0% (84–100%)
Tetracycline	23	43.5% (41–100%)
Erythromycin	23	56.5% (54–100%)
Meticillin	35	85.7% (85–100%)
Streptococcus pnuemoniae[21,22,57,58,60,79,88,92]		
Ampicillin	628	90.3% (64–100%)
Chloramphenicol	536	88.6% (74–100%)
Co-trimoxazole	487	61.4% (0–84%)
Ceftriaxone	127	100.0% (100%)
Ciprofloxacin	21	81.0% (60–100%)
Tetracycline	271	53.9% (50–70%)
Erythromycin	172	98.8% (90–100%)
***Salmonella enterica* serotype Typhi**[2,22,23,32,46,57]		
Ampicillin	813	89.1% (17–100%)
Chloramphenicol	813	92.0% (95–100%)
Co-trimoxazole	808	89.1% (0–100%)
Ceftriaxone	813	96.9% (97–100%)
Ciprofloxacin	813	97.1% (97–100%)
Gentamicin	43	95.3% (66–100%)
Tetracycline	41	65.8% (42–100%)
***S enterica* serotype Enteritidis**[2,22,23,57,79]		
Ampicillin	122	33.6% (0–96%)
Chloramphenicol	126	38.9% (0–100%)
Co-trimoxazole	88	93.2% (17–100%)
Ceftriaxone	112	100.0% (100%)
Ciprofloxacin	116	100.0% (100%)
Gentamicin	112	96.4% (66–100%)
Tetracycline	52	78.8% (17–100%)
***S enterica* serotype Typhimurium**[2,57,22]		

	Number of isolates*	Proportion of susceptible isolates (range of susceptibility)
Ampicillin	133	3.0% (0–100%)
Chloramphenicol	148	100.0% (100%)
Co-trimoxazole	133	15.0% (14–100%)
Ceftriaxone	133	977% (33–100%)
Ciprofloxacin	20	100.0% (100%)
Gentamicin	133	55.6% (0–100%)
Tetracycline	133	68.4% (0–100%)
Escherichia coli[2,22,23,57,92]		
Ampicillin	225	8.9% (4–83%)
Chloramphenicol	226	23.4% (10–83%)
Co-trimoxazole	71	16.9% (0–66%)
Ceftriaxone	71	100.0% (0–100%)
Ciprofloxacin	22	100.0% (100%)
Gentamicin	207	80.2% (0–93%)
Tetracycline	45	8.9% (0–10%)

*Cumulative number of isolates across cited studies with susceptibilities reported; not all studies tested susceptibilities to all listed antibiotics.

Table 5

Clinical and laboratory associations with non-malaria bloodstream infection from 12 studies, Africa, 1991-2006

	Reported positive association (p<0.05)	OR range, where reported*	Reported negative or no association
Lethargy or restlessness	Four paediatric studies[14,19,21,43]	OR 2.4–4.4[14,21,43]	..
Oral candidiasis	Two paediatric studies[14,21]	OR 1.8–7.2[4,14,21,46]	..
	2 adult studies[4,46]	..	..
Jaundice	One paediatric study[2]	OR 2.3–7.8[2,46]	..
	Two adult studies[4,46]	..	..
Splenomegaly	One paediatric study[2]	OR 1.7–2.5[2,4]	No association: three paediatric studies[14,21,43]
	One adult study[4]	..	..
Hepatomegaly	Two paediatric studies[4,14]	OR 2.0–5.0[4,14]	No association: one adult study[4]
Malnutrition or wasting	Four paediatric studies[14,21,48,92]	OR 1.8–7.3[14,21,48,92]	No association: one paediatric study[79]
		..	One adult study[23]
		..	Negative association: one paediatric study[2]
Fever >38.9°C	Two paediatric studies[14,19]	OR 21–4.4[4,14,46]	..
	Two adult studies[4,46]	..	..
Anaemia	Any BSI:† two paediatric studies[2,92]	Any BSI: OR 2.0[2,92]	..
	One adult study[23]	..	..
	Mycobacterial BSI: two adult studies[4,26]	Mycobacterial BSI: OR 9.5[4]	..
Leucopenia	White blood cells <5000 cells per mL: one adult study[4]	OR 2.1[4]	..
	White blood cells <1000 cells per mL: one adult study[23]	..	..
Leucocytosis >15 000 cells per mL	Two paediatric studies[14,43]	OR 2.4[14]	..

BSI=bloodstream infection.

*Comparison of the prevalence of the following findings among patients with BSI versus those without BSI; data from adult and paediatric studies are both presented in these ranges.

†Sigauque et al[92] found anaemia significant in multivariate, but not univariate, analysis.